Experimental Part

The compounds marked with an asterisk have been recently prepared by Kirkpatrick and Parker.[7] We have included descriptions of them here because of some differences in physical properties. The authors will be referred to as K. and P.

(7) Kirkpatrick and Parker, THIS JOURNAL, **57**, 1123 (1935).

Summary

The preparation of a series of amino alcohols derived from dibenzofuran is described. From 2-acetyldibenzofuran derivatives carrying the side chain —CHOH—CH_2NR_2 (NR_2 being the amino, dimethylamino, ethylamino, diethylamino and piperidino group) are obtained.

UNIVERSITY, VIRGINIA RECEIVED JULY 1, 1935

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. IX. Amino Alcohols Derived from 1,2,3,4-Tetrahydrophenanthrene[1]

BY ERICH MOSETTIG AND ALFRED BURGER

Morphine and most of its derivatives may be considered essentially as amino alcohols having the secondary alcoholic hydroxyl and the tertiary nitrogen attached to a partially hydrogenated phenanthrene nucleus. This consideration has led us in the past few years to the synthesis of a series of derivatives of phenanthrene and of partially hydrogenated phenanthrene carrying the side chains

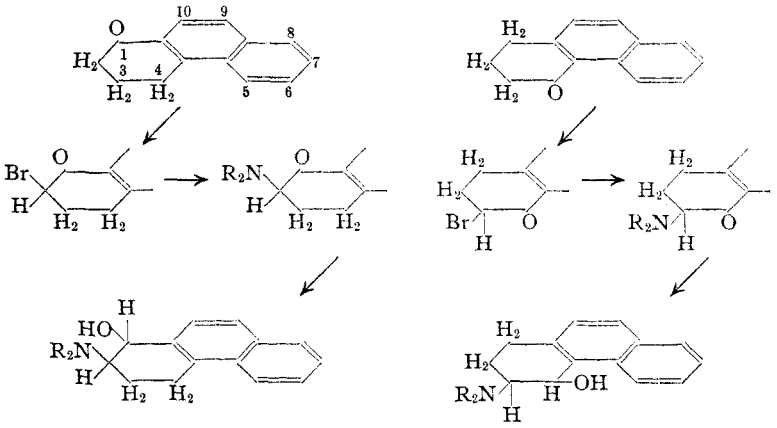
—CHOH—CH_2N= and —CHOHCH(—CH_3)—N=[2]

Some of the amino alcohols of this type show a decided pharmacological resemblance to morphine.[3]

This communication deals with a series of amino alcohols which differ principally from those mentioned above in that the alcoholic hydroxyl and the nitrogen are not located in a side chain, but are attached directly to carbon atoms of the phenanthrene nucleus itself, which must necessarily be hydrogenated in the ring carrying the substituents. It is apparent that the amino alcohols of this type are structurally somewhat more closely related to morphine and hence might be expected to show a morphine-like effect more pronounced than that of the open-chain amino alcohols.

The known 1-keto-1,2,3,4 - tetrahydrophenanthrene ("1-tetanthrenone"[4]) and the 4-isomer are convenient starting materials for the synthesis of a series of these new amino alcohols. The synthesis is outlined in the diagram.

The bromination of the tetanthrenones proceeds smoothly. The dimethylamino- and piperidino- ketones are formed in yields of over 80%,



NR_2 = dimethylamino-, diethylamino-, piperidino- and 1,2,3,4-tetrahydroisoquinolino-.

the corresponding tetrahydroisoquinolino compounds in yields of 60–70%. It is noteworthy that all attempts to exchange the bromine in the bromotetanthrenones with tetrahydroquinoline were without much success. In the reaction with diethylamine, whether carried out at room temperature or at elevated temperatures, the expected

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

(2) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933); van de Kamp and Mosettig, *ibid.*, **57**, 1107 (1935); Burger and Mosettig, *ibid.*, **56**, 1745 (1934).

(3) Unpublished results by Eddy and co-workers, University of Michigan.

(4) Trivial names introduced by G. Schroeter, *Ber.*, **57**, 2025 (1924).

TABLE I

No.	Derivatives of 1,2,3,4-tetrahydrophenanthrene	Solvent	Appearance	Yield, %	M. p., °C. (corr.)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
1	1-Keto-2-bromo-	MeOH	Colorless	90	84– 85	$C_{14}H_{11}BrO$							Br, 29.06	29.16
2	2-(Dimethylamino)-1-keto-hydrochloride	EtOH–ether	Little needles	75	218–220 (dec.)	$C_{16}H_{18}ONCl$					5.08	5.19		
3	-Picrate	EtOH	Yellow prisms		180 (dec.)	$C_{22}H_{20}O_8N_4$					11.97	12.18		
4	2-(Dimethylamino)-1-hydroxy-[a]	MeOH	Colorless		105–108	$C_{16}H_{19}ON$	79.62	79.43	7.94	7.98	5.81	6.02		
5	-Hydrochloride[b]	EtOH–ether	Colorless	91	223–224 (dec.)	$C_{16}H_{20}ONCl$					5.05	4.99	Cl, 12.77	12.54
6	-Benzoyl derivative hydrochloride[c]	EtOH–ether	Colorless		179–181 (dec.)	$C_{23}H_{24}O_2NCl$					3.67	3.68		
7	2-(Diethylamino)-1-keto-hydrochloride[d]	EtOH–ether	Colorless	33	143–148	$C_{18}H_{22}ONCl$	71.14	70.85	7.30	7.76	4.61	4.73		
8	2-(Diethylamino)-1-hydroxy-[e]		Colorless flakes		70– 72	$C_{18}H_{23}ON$	80.24	80.41	8.61	8.80				
9	-Hydrochloride[b]	EtOH–ether	Colorless flakes	59	221–223 (dec.)	$C_{18}H_{24}ONCl$					4.58	4.55	Cl, 11.60	11.75
10	-3,5-Dinitrobenzoyl deriv.[c]	EtOH	Slightly yellow		209–211 (dec.)	$C_{25}H_{25}O_6N_3$					9.07	9.08		
11	2-Piperidino-1-keto-[f]	MeOH	Yellow leaflets	81	138–140	$C_{19}H_{21}ON$					5.02	5.16		
12	-Hydrochloride	EtOH–ether	Colorless		236–238 (dec.)	$C_{19}H_{22}ONCl$					4.44	4.52		
13	2-Piperidino-1-hydroxy-[g]	EtOH	Colorless		121–126	$C_{19}H_{23}ON$	81.08	81.04	8.24	8.40	4.98	4.92		
14	-Hydrochloride	EtOH–ether	Colorless	95	259 (dec.)	$C_{19}H_{24}ONCl$	71.78	71.59	7.62	7.93	4.41	4.40	Cl, 11.16	11.33
15	2-(1,2,3,4-Tetrahydroisoquinolino)-1-keto-hydrochloride	EtOH–ether	Slightly yellow	56	226–227 (dec.)	$C_{23}H_{22}ONCl$					3.85	3.91		
16	2-(1,2,3,4-Tetrahydroisoquinolino)-1-hydroxy-[h]	Ether	Colorless		155–156	$C_{23}H_{23}ON$	83.85	84.04	7.04	7.38	4.26	4.41		
17	-Hydrochloride[b]	EtOH–ether	Colorless	91	227 (dec.)	$C_{23}H_{24}ONCl$					3.83	3.94	Cl, 9.70	9.66
18	3-Bromo-4-keto-	MeOH	Colorless prisms	87	104–105	$C_{14}H_{11}OBr$							Br, 29.06	28.85
19	3-(Dimethylamino)-4-keto-hydrochloride	EtOH–ether	Glittering leaflets	99	208–210 (dec.)	$C_{16}H_{18}ONCl$					5.08	5.06		
20	3-(Dimethylamino)-4-hydroxy-hydrochloride	EtOH–ether	Colorless	81	230 (dec.)	$C_{16}H_{20}ONCl$	69.16	69.02	7.26	7.36	5.05	5.26		
21	-Benzoyl derivative[c]	Dil. EtOH	Colorless		89– 90	$C_{23}H_{23}O_2N$	79.96	80.21	6.72	7.06	4.06	4.41		
22	-Benzoyl derivative hydrochloride	EtOH–ether	Colorless		177–178	$C_{23}H_{24}O_2NCl$					3.67	3.55		
23	3-(Diethylamino)-4-keto-hydrochloride	EtOH–ether	Colorless	28	184–185 (dec.)	$C_{18}H_{22}ONCl$					4.61	4.77		
24	-Picrate	EtOH	Yellow prisms		173–174 (dec.)	$C_{24}H_{24}O_8N_4$					11.29	11.32		
25	3-(Diethylamino)-4-hydroxy-hydrochloride	EtOH–ether	Colorless	78	239.5–240 (dec.)	$C_{18}H_{24}ONCl$	70.67	70.54	7.91	8.13	4.58	4.45		
26	-Picrate	EtOH	Yellow needles		206–208 (dec.)	$C_{24}H_{26}O_8N_4$					11.25	11.13		
27	-Benzoyl deriv. picrate[c]	EtOH	Large yellow needles		173–174 (dec.)	$C_{31}H_{30}O_9N_4$					9.30	9.36		
28	-3,5-Dinitrobenzoyl deriv.[c]	EtOH	Faintly yellow		216–217.5	$C_{25}H_{25}O_6N_3$					9.07	9.00		
29	3-Piperidino-4-keto-hydrochloride	EtOH–ether	Colorless	81	248–250 (dec.)	$C_{18}H_{22}ONCl$					4.44	4.47		
30	3-Piperidino-4-hydroxy-hydrochloride	EtOH–ether	Colorless	87	246–247 (dec.)	$C_{19}H_{24}ONCl$	71.78	71.74	7.62	7.91	4.41	4.68		
31	-Benzoyl derivative hydrochloride[c]	EtOH	Fine		181–182 (dec.)	$C_{26}H_{28}O_2NCl$					3.32	3.39		
32	3-(1,2,3,4-Tetrahydroisoquinolino)-4-keto-hydrochloride		color-	69	164–166 (dec.)	$C_{23}H_{22}ONCl$					3.85	3.90		
33	-Perchlorate	MeOH	less		210 (dec.)	$C_{23}H_{22}O_6NCl$					3.28	3.35		
34	3-(1,2,3,4-Tetrahydroisoquinolino)-4-hydroxy-hydrochloride[b]	EtOH–ether	needles	80	230–231 (dec.)	$C_{23}H_{24}ONCl$	75.48	75.15	6.62	6.72	3.83	3.97		
	Substance													
35	1-Hydroxyphenanthrene[i,j]	Dil. EtOH	Colorless		153	$C_{14}H_{10}O$	86.56	86.55	5.19	5.33				
36	$C_{14}H_9OH \cdot OC_{14}H_{13}$[i,k]	MeOH	Colorless		119	$C_{14}H_{11}O$	86.11	86.05	5.68	5.53				
37	4-Hydroxyphenanthrene[l]	Bz–lig.	Colorless		113	$C_{14}H_{10}O$	86.56	86.54	5.19	5.41				
38	$C_{14}H_9OH \cdot OC_{14}H_{13}$[l,m]	MeOH	Colorless		107	$C_{14}H_{11}O$	86.11	85.99	5.68	6.01				

[a] Sinters at 95°, purified by high vacuum sublimation at 90°. [b] The carbon value of this compound was always found about 1% low. [c] Benzoyl and 3,5-dinitrobenzoyl derivatives of amino alcohols were prepared by allowing the hydrochlorides of the bases to stand with the calculated amount of the acyl chloride in pyridine solution at room temperature. [d] The crude hydrochloride was converted to the perchlorate or benzoate through the base and reconverted to the hydrochloride. It sinters at 138° and is completely melted at 156°. [e] Purified by high vacuum distillation at 90°, melts unsharply, begins to soften at 60°. [f] The amino ketone is sparingly soluble in benzene and separates from the reaction mixture. [g] Purified by high vacuum sublimation at 105°. Completely melted at 132°. Gives no benzoyl or dinitrobenzoyl derivative. [h] Gives no benzoyl derivative. [i] Formed as by-product in the preparation of No. 7 and in very small amount in that of No. 2, also in about 50% yield on boiling 2-bromo-1-tetranthrenone with diethylaniline for 4 hours. [j] Identical with 1-hydroxyphenanthrene obtained by heating 1-tetanthrenone with powdered selenium for fourteen hours at 295° (yield, 25%). [k] Molecular weight determination by the Rast method: found, 198, 189; by cryoscopic method in *p*-chlorotoluene, found, 193. Calculated for $C_{14}H_{11}O$, mol. weight 195. Semicarbazide acetate yields under the usual conditions, the semicarbazone of

1-tetanthrenone; 1-hydroxyphenanthrene is found in the mother liquors of the semicarbazone. Dilute potassium hydroxide solution extracts 1-hydroxyphenanthrene from the ethereal solution of the molecular compound decidedly slower than from an equally concentrated control solution of 1-hydroxyphenanthrene. Obtained also by boiling 2-bromo-1-tetanthrenone with diethylaniline as above (yield 30%). [l] Formed as by-product in the preparation of No. 23. [m] Prepared also by allowing molecular quantities of 4-hydroxyphenanthrene and 4-tetanthrenone to crystallize from methanol.

amino ketones are formed in yields of only about 20–30%. In the 1,2-series, 1-hydroxyphenanthrene and another nitrogen-free compound melting at 119° can be isolated from the reaction mixture in a total yield of about 25%. The compound of m. p. 119° sublimes readily at 90° in a high vacuum, and is converted to 1-hydroxyphenanthrene and 1-tetanthrenone by short warming with alcoholic potassium hydroxide. It is apparently a molecular compound and can also be obtained by crystallizing the two components in molecular quantities from methyl alcohol. The molecular compound shows a molecular weight corresponding to the simple formula $C_{14}H_{11}O$. The hydroxyphenanthrene is obviously formed by the loss of hydrogen bromide from the bromo ketone; we have no explanation at present for the formation of the tetanthrenone, the other constituent of the molecular compound. Auwers and Lämmerhirt[5] and later Krollpfeiffer and Schäfer[6] isolated from the reaction of α-halogenated ketones with diethylaniline, the corresponding bromine-free ketones in varying amounts, but offered no explanation for this peculiar reductive action of the amine. When we allowed 1,2-bromotetanthrenone to react with diethylaniline, 1-hydroxyphenanthrene (50%) and the molecular compound of m. p. 119° (30%) were formed. Neither in this reaction nor in that with diethylamine could any free tetanthrenone be found. The reaction of the 3,4-bromotetanthrenone proceeds throughout like that of the 1,2-isomer. In addition to the desired amino ketone, 4-hydroxyphenanthrene and a molecular compound (1 mole of 4-hydroxyphenanthrene with 1 mole of 4-tetanthrenone) can be isolated.

The amino ketones were reduced catalytically (platinum oxide) to the corresponding amino alcohols. In all cases only one of the two possible diastereomeric forms was obtained.

1,2,3,4-Tetrahydrophenanthrene is pharmacologically more effective in all respects, and especially in analgesic action, than either phenanthrene or 1,2,3,4,5,6,7,8-octahydrophenanthrene.[3] Of the two tetanthrenones the 1-keto isomer behaves quite unusually. In sufficient doses it shows a marked and mounting (up to five hours) analgesic action without showing much other effect. The 4-keto isomer is far less effective,[3] a relationship which is also known to hold true in the relative oestrogenic activity of these two isomers.[7]

The cyclic amino alcohols are generally more analgesic than the ones with the open side chain —CHOH—CH_2N= and —CHOH—CH(—CH_3)—N=. It is remarkable that two of them approach and even excel some of the morphine derivatives. The effective analgesic dose of 2-piperidino-1-hydroxy-1,2,3,4-tetrahydrophenanthrene is 20 mg. per kg.; the corresponding dose of the 3-tetrahydroisoquinolino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene is 15 mg. per kg., comparable with the effective doses of 10 and 20 mg. for codeine and pseudocodeine, respectively.[3]

We are indebted to Mr. Lyon Southworth of this Laboratory for the analyses appearing in this paper.

Experimental Part

Bromotetanthrenones.—Bromine (one mole) was added slowly to a solution or suspension of finely powdered tetanthrenone in absolute ether containing a few drops of ethereal hydrogen chloride. The bromine was taken up rapidly and the bromo ketone either crystallized out or was obtained by distilling the ethereal solution after washing it with water.

Amino Ketones.—A benzene solution of the bromo ketone (one mole) and the respective amine (3 moles) was allowed to stand in a stoppered flask at room temperature for two days. The color of the mixture became gradually yellow and deepened to dark red in some cases. The precipitation of the amine hydrobromide indicates the progress of the exchange. The reaction mixture was diluted with ether, the amine hydrobromide removed with water and the solution evaporated *in vacuo*. The residue was dissolved in acetone and the amino ketone hydrochloride precipitated with ethereal hydrogen chloride. The replacement of the bromine atom by the diethylamine residue proceeds only very slowly at room temperature. Therefore the benzene solution of the components was heated to 100° in a sealed tube for twenty-four hours, poured into dilute hydrochloric acid, and the non-basic reaction products were extracted into ether. The amino ketone hydrochloride crystallized partly from the aqueous solution.

(5) Auwers and Lämmerhirt, *Ber.*, **53**, 428 (1920).
(6) Krollpfeiffer and Schäfer, *ibid.*, **56**, 620 (1923).
(7) Cook, Dodds, Hewett and Lawson, *Proc. Roy. Soc.* (London), Series B, **114**, No. B, 788, 272 (1934).

Another portion of the amino ketone was obtained from the filtrate in the usual way. The amino ketone hydrochloride was separated from small amounts of high-melting, very insoluble, crystalline by-products by crystallization from alcohol. The ether–benzene solution of the indifferent by-products was evaporated and the residue sublimed in a high vacuum at 90–100°, whereby half of it remained as a tar in the distilling flask. The distillate was separated by crystallization from alcohol. The molecular compounds (m. p. 119 and 107°, respectively) are less soluble than the corresponding phenanthrols. In order to avoid distillation, the residue was repeatedly crystallized from alcohol and ligroin in another experiment; the results were essentially the same. The total yield of crystalline reaction products was about 50%.

Amino Alcohols.—The amino ketone hydrochlorides of the 3,4-series could be hydrogenated in methyl alcoholic solution with a platinum oxide catalyst to the corresponding amino alcohols without any complication. The success of the hydrogenation of the amino ketone hydrochlorides of the 1,2-series with platinum oxide depends apparently upon uncontrollable factors. In some cases the calculated amount of hydrogen was absorbed, and the amino alcohols could be isolated in a pure state; in other cases considerably more hydrogen, up to two moles, was absorbed and the amino alcohol hydrochlorides could be separated from the reaction mixture only in small amounts. However, satisfactory results were obtained consistently by hydrogenating the free amino ketones in methanol solution.

Summary

The synthesis of a series of amino alcohols derived from tetrahydrophenanthrene is described. This new type of amino alcohol is characterized by having the alcoholic hydroxyl and the nitrogen directly attached to the phenanthrene nucleus.

The synthesis is effected by exchanging the bromine atoms in 1-keto-2-bromo-1,2,3,4-tetrahydrophenanthrene and in 3-bromo-4-keto-1,2,3,4-tetrahydrophenanthrene with the dimethylamino, diethylamino, piperidino and tetrahydroisoquinolino group, and reducing the resulting amino ketones catalytically to the corresponding amino alcohols.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. II. The Hydrocarbon Synthesis[1]

BY LOUIS F. FIESER AND EMANUEL B. HERSHBERG

The most prominent synthetical routes to members of the phenanthrene series were developed in order to provide methods of identifying degradation products of certain opium alkaloids, resin acids and natural products containing the aetiocholane ring system. The Pschorr synthesis,[2] the phenanthrene syntheses of Bardhan and Sengupta[3] and of Bogert,[4] which employ a common intermediate, and the method of cyclizing suitable arylbutyric acids, which has received particular elaboration in the hands of R. D. Haworth,[5] have been employed further by Cook, in the course of his important work on the cancer problem for the preparation of polynuclear hydrocarbons containing the phenanthrene nucleus.[6] The interest in synthetic compounds of possible sex hormone activity has provided a further impetus for the exploitation of the known methods and for the development of new avenues of approach.

The diene reaction of Diels and Alder has until very recently[6a] found little application to the problem.

Although hydrophenanthrene derivatives would be expected to result from the addition of dienes to β-naphthoquinones, a successful reaction of this type has been reported only in the case of one alkylated quinone,[7] and the reaction is not such as to lend itself to general application. A difficulty in the case of the ortho quinones is that they are perhaps too reactive, and too prone to enter into complicating side reactions. 3,4-Dihydronaphthalene-1,2-dicarboxylic acid anhydride (I), which is but one example of a class of compounds readily available by the Bougault synthesis,[8] is far more stable than the quinones, and, being a cyclic derivative of maleic anhydride, is of a type theoretically amenable to condensation with di-

(1) Preliminary communication: THIS JOURNAL, **57**, 1508 (1935).

(2) Pschorr, *Ber.*, **29**, 496 (1896).

(3) Bardhan and Sengupta, *J. Chem. Soc.*, 2520, 2798 (1932).

(4) Bogert, *Science*, **77**, 289 (1933).

(5) Haworth and co-workers, *J. Chem. Soc.*, 1125, 1784, 2248, 2717, 2720 (1932); 454 (1934).

(6) Cook, *ibid.*, 1472 (1932); Cook and Hewett, *ibid.*, 398 (1933); Cook, Haslewood and Robinson, *ibid.*, 667 (1935); Cook and Haslewood, *ibid.*, 767 (1935).

(6a) Barnett and and Lawrence, *J. Chem. Soc.*, 1104 (1935).

(7) Fieser and Seligman, THIS JOURNAL, **56**, 2690 (1934).

(8) Fieser and Hershberg, *ibid.*, **57**, 1851 (1935).